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Body Mass Index and Magnetic Resonance Markers of Brain Integrity in Adults

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Abstract

Objective—Obesity and being overweight during adulthood have been consistently linked to increased risk for development of dementia later in life, especially Alzheimer's disease. They have also been associated with cognitive dysfunction and brain structural alterations in otherwise healthy adults. Although proton magnetic resonance spectroscopy may distinguish between neuronal and glial components of the brain and may point to neurobiological mechanisms underlying brain atrophy and cognitive changes, no spectroscopic studies have yet assessed the relationships between adiposity and brain metabolites.

Methods—We have utilized magnetic resonance imaging and proton magnetic resonance spectroscopic imaging data from 50 healthy middle-aged participants (mean age, 41.7 ± 8.5 years; 17 women), who were scanned as control subjects for another study.

Results—After adjustment for age and sex, greater body mass indices (BMIs) correlated with: (1) lower concentrations of *N*-acetylaspartate (spectroscopic marker of neuronal viability) in frontal ($p = 0.001$), parietal ($p = 0.006$), and temporal ($p = 0.008$) white matter; (2) lower *N*-acetylaspartate in frontal gray matter ($p = 0.01$); and (3) lower concentrations of choline-containing metabolites (associated with membrane metabolism) in frontal white matter ($p = 0.05$).

Interpretation—These results suggest that increased BMI at midlife is associated with neuronal and/or myelin abnormalities, primarily in the frontal lobe. Because white matter in the frontal lobes is more prone to the effects of aging than in other lobes, our results may reflect accelerated aging in individuals with high levels of adiposity. Thus, greater BMI may increase the odds of developing an age-related disease, such as Alzheimer's disease.

Brain atrophy and lower concentration of *N*-acetylaspartate (NAA; marker of neuronal viability), especially in temporal lobes and hippocampus, are among risk factors for cognitive decline and dementia in elderly adults.^{1,2} Recent epidemiological studies have associated midlife adiposity with increased risk for dementia later in life, especially Alzheimer's disease (AD).^{3,4} In particular, they made the following associations: (1) atrophy of temporal lobes and

greater prevalence of dementia in elderly women with consistently greater body mass index (BMI; an indicator of body adiposity) throughout adulthood⁵; (2) brain atrophy with greater BMI in male and female adults in their 50s⁶; and (3) smaller hippocampal volumes in elderly adults with larger waist/hip ratio (a measure of body fat distribution).⁷ Moreover, several epidemiological studies have identified increased BMI in middle age as a risk factor for diagnosis of dementia a few decades later, especially in women.^{8–10} These studies generally accounted for comorbid conditions such as hypertension, diabetes mellitus, among others,⁴ suggesting that body fat necessarily has detrimental effects on brain integrity and function. Adiposity appears to have functional relevance because studies found worse learning, memory, and executive functioning in obese versus nonobese older adults.^{11–13} In addition, Gunstad and colleagues,¹⁴ in a study among young and middle-aged healthy adults, associated being overweight or obese with executive dysfunction.

Alterations of brain morphology were also found in overweight and obese young adults.¹⁵ Pannacciulli and coworkers¹⁵ demonstrated focal gray matter (GM) volume reductions especially in frontal lobe accompanied by enlarged volumes of orbitofrontal white matter (WM), whereas Haltia and coworkers¹⁶ demonstrated only significantly enlarged WM volumes in several basal brain regions that got smaller with dieting. This suggests that brain neurobiological and functional alterations in individuals with high levels of adiposity may be present decades before the onset of dementia.

Given there are 1 billion overweight and 300 million obese individuals worldwide,¹⁷ and considering the significantly increasing prevalence of these conditions worldwide¹⁸ and in the United States,¹⁹ research into the effects of adipose tissue on the brain may play a significant role in understanding the processes that lead to dementia.

Although proton magnetic resonance spectroscopy can distinguish between neuronal and glial components of the brain and give insight into brain metabolism, no studies have assessed the association between any markers of adiposity at middle age and spectroscopic markers of brain integrity. We used proton magnetic resonance spectroscopic imaging at short-echo time to measure the concentrations of four major brain metabolites^{20,21}: (1) NAA, an accepted marker of neuronal viability, observed only in mature neurons and their processes, decreased NAA reflects neuronal loss, atrophied dendrites and axons, and/or derangements in neuronal energetics; (2) choline-containing compounds (Cho), which are believed to be primarily involved in cell membrane breakdown and synthesis; (3) creatine-containing metabolites (Cr) involved in cell bioenergetics; and (4) myo-inositol (m-Ino), which is considered a marker of glial cell numbers and an osmoregulator.

Given the epidemiological associations between midlife adiposity and risk for dementia later in life, the cognitive and neurobiological abnormalities in individuals with high levels of adiposity may reflect risk factors and/or processes that lead to dementia. To further these results, we evaluated the relationships of self-reported BMI to mean concentrations of NAA, Cho, Cr, and m-Ino in GM and WM of the frontal, parietal, temporal, and occipital lobes and to GM, WM, and cerebrospinal fluid volumes of these lobes in a group of healthy middle-aged adults.

Subjects and Methods

Subjects

Fifty healthy middle-aged (mean age, 41.7 ± 8.5 years) individuals (17 women, 34%) were recruited from the San Francisco Bay Area. They served as human immunodeficiency virus–negative control participants in a study describing the effects of human immunodeficiency virus and alcohol use disorder on the central nervous system.^{22,23} They were free of any

medical conditions known or suspected to affect brain morphology and metabolism, and drank less than 40 standard alcoholic drinks per month. A standard drink contains 13.6g of pure ethanol, equivalent of 12 ounces beer, 5 ounces wine, or 1.5 ounces liquor. BMI was calculated as weight in kilograms divided by height in meters squared that were obtained by self-report. BMI ranged between 18.7 and 36.8kg/m²; that is, participants were at normal weight (18.5 < BMI < 25), overweight (25 < BMI < 30), or obese (BMI > 30). The American National Adult Reading Test estimated verbal intelligence,²⁴ and Beck Depression Inventory assessed current depressive symptomatology.²⁵ Alcohol consumption was assessed via lifetime drinking history.²⁶ Frequency of cigarette smoking over 6 months before study was assessed with an in-house self-report questionnaire. Participants were considered smokers if they reported smoking more than twice a month. All participants gave written informed consent to all procedures approved by the institutional review boards of the University of California San Francisco and the San Francisco Veterans Affairs Medical Center.

Data Acquisition and Processing

All magnetic resonance data were obtained on a standard 1.5-Tesla magnetic resonance system (Siemens Vision, Iselin, NJ). Structural magnetic resonance imaging data were obtained with magnetization-prepared, rapid, gradient-echo images acquired with TR/TE/TI = 10/7/300 milliseconds, 15-degree flip angle, oblique-coronal, 1 × 1mm² in-plane resolution, and 1.5mm-thick coronal partitions yielded T1-weighted images. Magnetic resonance imaging was followed by automated head shimming and multislice short-TE proton magnetic resonance spectroscopic imaging (TR/TE/TI = 1,800/25/165 milliseconds).²⁷ Spectra were acquired in 3 oblique-axial parallel planes, each 15mm thick, and 6mm apart. For structural analyses, probability maps of GM, WM, and cerebrospinal fluid within frontal, parietal, temporal, and occipital lobes were obtained from T1-weighted images by combining three-tissue probabilistic segmentation and masks of major lobes as previously described.²² Processing details for spectroscopic data were described previously.^{23,28} The outcome measures were absolute, mean, atrophy-corrected metabolite concentrations for two tissue types (GM and WM) in four major lobes. They were expressed in institutional units, not in molar units, to avoid possibly inaccurate assumptions about relaxation times.

An experienced neuroradiologist examined all images for evidence of any cerebrovascular disease or structural abnormalities. No participant had early confluent or confluent areas of WM signal hyperintensities. The volumes of WM signal hyperintensities were estimated to be less than 1% of the individual's total WM volume.²⁹

Statistical Analysis

To account for age-related decreases in brain volumes,³⁰ age-related increases in BMI⁵ (in our cohort, greater BMI tended to correlate with older age at $p = 0.21$; $p = 0.07$), and potential age-related changes in metabolite concentrations,³¹ we utilized a linear modeling approach, with BMI, age, and sex used as predictor variables. To control for interparticipant differences in head size, we used total intracranial volume, defined as sum of all GM, WM, and cerebrospinal fluid volumes, as predictor of brain volumes. Sex by BMI interactions (accounting for potentially larger effects of adiposity on the female brain) were not significant for any brain volume or any metabolite concentration in any region and were not included in the model.

To correct for multiple comparisons, we multiplied the significance levels of BMI and sex by the number of evaluated regions for each metabolite (GM and WM in four major lobes = eight regions). For volumetric measures, the significance levels for BMI were not corrected for multiple comparisons and are reported only for qualitative comparison with other studies. A

significance level of $p < 0.05$ (after correction for multiple comparisons) was considered statistically significant.

For illustration, we also report Spearman's correlation coefficients between magnetic resonance measures and BMI. All analyses were implemented in S-PLUS 6.0 (Insightful Corporation, Seattle, WA) and SPSS-12.0 for Windows (SPSS, Chicago, IL).

Results

Ten percent of our study participants was classified as obese ($\text{BMI} > 30$; $n = 5$; 3 women), 30% overweight ($25 < \text{BMI} < 30$; $n = 15$; 4 women), and 60% were at normal weight ($18.5 < \text{BMI} < 25$; $n = 30$; 10 women). No participant was classified as underweight. Seventy-two percent of participants was white, 12% Latino, and 6% Asian. One participant was black, one Polynesian, and three participants did not disclose their ethnicities. Men and women had similar age, education level, and BMI. There were no significant differences in age, education level, American National Adult Reading Test score, current depressive symptomatology (Beck Depression Inventory), and height among participants classified as normal, overweight, or obese (all $p > 0.25$; compare Table). Kolmogorov–Smirnov tests demonstrated that the distributions of the metabolite concentrations and volumes did not significantly depart from normality.

Greater BMI (Fig) was associated with lower NAA concentrations in frontal ($p = 0.001$), parietal ($p = 0.006$), and temporal WM ($p = 0.008$). Greater BMI also related to lower NAA concentration in frontal GM ($p = 0.01$) and to lower Cho concentration in frontal WM ($p = 0.05$) (all p values were Bonferroni corrected for multiple comparisons across regions). In the linear model fit, BMI accounted for the following amounts of variance: 25% for frontal WM NAA, 20% for parietal WM NAA, 17% for temporal WM NAA, 15% for frontal GM NAA, and 20% for frontal WM Cho. The corresponding Spearman's correlation coefficients were as follows: $\rho = -0.62$ for frontal WM NAA; $\rho = -0.55$ for parietal WM NAA; $\rho = -0.52$ for temporal WM NAA; $\rho = -0.43$ for frontal WM Cho; and $\rho = -0.48$ for frontal GM NAA (all $p < 0.02$ after Bonferroni correction for multiple comparisons across regions). These correlations were similar among men and women. The other regional metabolite concentrations were not associated with BMI.

Greater BMI was potentially associated with smaller parietal GM volume ($p = 0.03$, uncorrected) and larger frontal WM volume ($p = 0.04$, uncorrected). Female sex was significantly associated with 5 and 4% greater NAA in frontal GM and WM, respectively, as well as 3% greater frontal WM Cr (all $p < 0.03$, after correction for multiple comparisons). However, previous studies comparing absolute metabolite concentrations between male and female individuals used long echo time ($\text{TE} > 135$ milliseconds) and did not yield consistent results.^{32–35}

In addition, to assess robustness of the results to the models used, we repeated all analyses with additional predictors: (1) age-squared term to evaluate possible nonlinear effects in aging,³⁰ (2) mean regional GM contributions to spectroscopic voxels to control for partial-volume effects,³⁶ (3) smoking status to partial out the potential detrimental effect of smoking on the outcome measures,^{37,38} and (4) average number of alcoholic drinks per month over lifetime and over the year preceding the study, as well as American National Adult Reading Test score and years of education. Moreover, to account for potential spurious associations between participant's body shape (weight, height), specific absorption rate, B_1 inhomogeneities, and so forth and measured metabolite concentrations, we used Cr as a covariate in the model, because it would be affected by these factors in a way similar to the other metabolites given the flat excitation profile of the pulses over the spectral range. None of these additional covariates

significantly affected the results. Finally, when BMI was removed from the models, that is, the predictors were age and sex only, the age dependence of magnetic resonance measures did not change significantly, which confirms that the reported associations between magnetic resonance measures and BMI were not statistically mediated by BMI increasing with age.

Discussion

The major finding of this study was that greater BMI was significantly associated with the following characteristics: (1) lower NAA concentrations in frontal, parietal, and temporal WM; 2) lower NAA concentration in frontal GM; and 3) lower Cho concentration in frontal WM. No significant associations of BMI with lobar brain volumes or regional concentrations of Cr or m-Ino were detected.

Lower NAA is consistent with derangement of neurometabolism, lower dendritic/axonal density, and/or axonal loss. Lower Cho in frontal WM suggests membrane and/or myelin alterations and/or alterations in membrane turnover. Thus, these results point to axonal and myelin abnormalities in frontal, parietal, and temporal WM, as well as decreased neuronal viability in the frontal lobe that are associated with greater BMI. This pattern of associations is not consistent with regions demonstrating volumetric and spectroscopic changes in preclinical³⁹ and symptomatic AD.⁴⁰ Spectroscopic studies in AD consistently demonstrated lower NAA^{40,41} and greater m-Ino⁴² levels in GM of medial temporal lobe and parietal lobes, but reports about Cho were inconclusive.⁴³ Nevertheless, given the epidemiological associations between midlife adiposity and increased chances of AD, our results suggest that some processes leading to AD may have their origin in WM.

The strongest associations of BMI with NAA and Cho concentrations in the brain were found in the frontal WM, a region that myelinates later than the other lobes and is thought to be more prone to damage during aging.⁴⁴ Consistently, age-related decreases of fractional anisotropy (a diffusion marker of WM microstructural fiber integrity) are also more pronounced in anterior versus posterior WM.³¹ This suggests that our results may reflect accelerated aging of WM in individuals with high levels of adiposity. Alternatively, because overweight or obese adults are likely to be overweight or obese as children,⁴⁵ our findings could also reflect the adverse effects of adipose tissue¹⁰ on brain development. Taken together, our data suggest that adiposity has an adverse impact on aging and/or developmental processes of the brain, and thus may increase the odds of aging-related diseases such as AD. In addition, virtually identical relationships between BMI and metabolite concentrations in male and female individuals (reflected through insignificant interactions between BMI and sex) suggest that independent risk factors/processes explain why obese women appear to be more vulnerable to the development of late-life dementia than do men.

Based on many epidemiological studies, our results of frontal metabolic abnormalities with greater BMI may reflect increased risk for development of dementia later in life, possibly linked to compromised neuronal energetics.²⁰ Stokin and colleagues⁴⁶ demonstrated axonal transport defects and axonal swelling in mice models of AD and occasionally in aged wild-type mice, which preceded amyloid deposition by at least 1 year (this corresponds to several decades in human life). They also identified similar axonal defects in postmortem brains from individuals who showed early symptoms of AD but no amyloid plaques.⁴⁶ This axonal swelling might be consistent with our findings of larger frontal WM volume with greater BMI (insignificant after correction for multiple comparisons), and with reports of associations between greater BMI and enlarged WM volume in young overweight and obese individuals.^{15,16}

NAA abnormalities may also reflect insulin dysregulation (insulin resistance or hyperinsulinemia) that is often found among obese individuals.⁴⁷ This dysregulation leads to reduced insulin transport into the brain, which results in impaired glucose utilization⁴⁷ that could be associated with lower NAA.⁴⁸ However, given the relatively small number of obese participants in our study, we do not believe that this mechanism explains our findings.

The limitations of our study include lack of assessment of potentially important covariates, such as total cholesterol, systolic and diastolic blood pressure, glucose and insulin levels, family history of AD, and apolipoprotein E genotype. However, in epidemiological studies, apolipoprotein E ϵ 4 did not correlate with BMI⁸ and did not explain the associations between greater BMI and smaller brain volumes.⁶ Other markers of body fat and its distribution, potentially more strongly associated with brain abnormalities, such as waist/hip ratio or waist circumference,⁴ were not available for our analyses. Finally, potential unrecorded group differences in nutrition, stress, exercise and general fitness, overall physical health, and genetic predispositions (other than via apolipoprotein E) may contribute to the results described in this study.

In summary, this study is the first to demonstrate that greater BMI in otherwise healthy middle-aged adults is associated with axonal and/or myelin abnormalities in WM, primarily in the frontal lobe, and with neuronal injury in frontal GM. Because WM in the frontal lobes is more prone to the effects of aging than in other lobes, our results may reflect accelerated aging in individuals with high levels of adiposity, which may be associated with greater probabilities of development of AD. Significant associations of BMI with regional brain metabolite concentrations and with lobar brain volumes (the latter insignificant after correction for multiple comparisons) suggest that neuronal/glial metabolic abnormalities precede volumetric changes that may become detectable later in life or in individuals with more adipose tissue. Our findings extend previous associations between brain structure and adiposity. However, the data did not allow us to discern whether these abnormalities were associated with body fat per se, comorbid conditions, nutrition, or sedentary lifestyle. If our observations are confirmed in prospective studies that control for other important factors associated with adiposity, they may help understand important neurobiological changes preceding late-life dementia.

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Fig. Concentrations of N-acetylaspartate (NAA; marker of neuronal viability, in institutional units [i.u.]) as a function of body mass index (BMI), separately for men (solid circles) and women (open circles). The relationships were not covaried for age, which was a nonsignificant factor in the model. GM = gray matter; WM = white matter.

Table

Comparison of Demographic Variables between Participants Classified as Normal, Overweight, and Obese

Variables	Normal	Overweight	Obese
n (female sex)	30 (10)	15 (4)	5 (3)
Age, yr	40.4 ± 9.3	44.0 ± 7.6	44.9 ± 7.2
Education, yr	15.5 ± 2.2	15.7 ± 2.2	15.4 ± 1.8
Height, m	1.74 ± 0.10	1.75 ± 0.07	1.69 ± 0.14
Weight, kg	67.6 ± 8.2	83.5 ± 8.6	93.9 ± 22.7
BMI, kg/m ²	22.4 ± 1.7	27.2 ± 1.7	32.4 ± 2.6
Average number of alcoholic drinks per month over lifetime	9.98 ± 9.74	14.5 ± 8.4	20.8 ± 17.6
Average number of alcoholic drinks in the week before study	1.15 ± 1.18	1.33 ± 0.75	1.24 ± 0.77
AMNART score	1.22 ± 0.47	1.28 ± 0.41	1.16 ± 0.72
BDI score	5.4 ± 5.4	4.8 ± 6.7	7.2 ± 7.0
Smoker, n ^a	5	1	2
Daily smoker, n	1	0	1

^aReported smoking at least twice a month.

BMI = body mass index; AMNART = American National Adult Reading Test; BDI = Beck Depression Inventory